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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/68, C12P 19/34, C07H 21/04, A61K 16/00, G01N 33/53		A1	(11) International Publication Number: WO 00/08210
			(43) International Publication Date: 17 February 2000 (17.02.00)
(21) International Application Number: PCT/US99/16811			(74) Agents: LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(22) International Filing Date: 22 July 1999 (22.07.99)			
(30) Priority Data: 60/095,232 4 August 1998 (04.08.98) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/095,232 (CIP) Filed on 4 August 1998 (04.08.98)			
(71) Applicant (for all designated States except US): DIADEXUS LLC [US/US]; 3303 Octavius Drive, Santa Clara, CA 95054 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): SUN, Yongming [CN/US]; Apartment 260, 869 S. Winchester Boulevard, San Jose, CA 95128 (US). RECIPON, Herve [FR/US]; 85 Fortuna Avenue, San Francisco, CA 94115 (US). CAFFERKEY, Robert [IE/US]; Apartment 218, 350 Elan Village Lane, San Jose, CA 95134 (US).			
(54) Title: A NOVEL METHOD OF DIAGNOSING, MONITORING, STAGING, IMAGING AND TREATING BREAST CANCER			
(57) Abstract The present invention provides a new method for detecting, diagnosing, monitoring, staging, prognosticating, imaging and treating breast cancer.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16811

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 435/6, 7.1, 91.2; 536/23.5, 24.31; 424/174.1; 530/388.1, 388.8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 7.1, 91.2; 536/23.5, 24.31; 424/174.1; 530/388.1, 388.8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,668,267 A (WATSON et al) 16 September 1997, columns 6 and 7.	1-5
Y	WO 98/18945 A (ABBOTT LABORATORIES) 07 May 1998, pages 4, 7, 46 and 87.	1-5, 7, 9
X	US 5,759,776 A (SMITH et al) 02 June 1998, column 16.	1

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 SEPTEMBER 1999

Date of mailing of the international search report

20 OCT 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CARLA MYERS

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16811

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C12Q 1/68; C12P 19/34; C07H 21/04; A61K 16/00; G01N 33/53

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

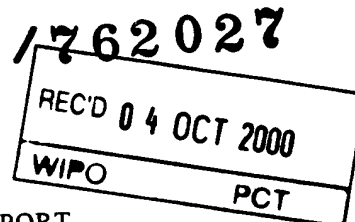
APS; WEST Derwent files; DIALOG: Medline, Biosis, Embase, Scisearch, CA; GenBank/EMBL, n-gene seq
search terms: breast, mammary, tumor, carcinoma, cancer, mRNA, protein, antibody, SEQ ID NO: 1-5

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference DEX-0040	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/16811	International filing date (day/month/year) 22 JULY 1999	Priority date (day/month/year) 04 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant DIADEXUS LLC		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 29 FEBRUARY 2000	Date of completion of this report 05 SEPTEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CARLA MYERS  Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/16811

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:

pages 1-31, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the claims:

pages 32-34, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the drawings:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages 1-7, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig. NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/16811

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)

Claims	<u>6-14</u>	YES
Claims	<u>1-5</u>	NO

Inventive Step (IS)

Claims	<u>6, 8, 10-14</u>	YES
Claims	<u>1-5, 7, and 9</u>	NO

Industrial Applicability (IA)

Claims	<u>1-14</u>	YES
Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-5 lack novelty under PCT Article 33(2) as being anticipated by Watson et al (herein after 'Watson'). Watson teaches methods for diagnosing breast cancer by detecting levels of mammaglobin mRNA in tissues or bodily fluids of a patient and comparing the levels of mammaglobin to those obtained in control, normal tissues or bodily fluids wherein the presence of increased levels of mammaglobin is indicative of the presence of breast cancer (see, for example, col. 6, and 8-9). Watson teaches that mammaglobin is expressed in tumor and normal breast tissue, but is not expressed in non-breast tissues (col. 6). Accordingly, mammaglobin is considered to be a breast specific gene (BSG). Watson (col. 6) further teaches that detection of mammaglobin can be used to diagnose metastatic breast cancer and to stage breast cancer.

Claims 1-5, 7 and 9 lack an inventive step under PCT Article 33(3) as being obvious over Abbott Laboratories. Abbott Laboratories teaches nucleic acids comprising the BS106 gene and sequences having at least 50% identity with this gene and thereby teaches nucleic acids which comprises a sequence identical to instant SEQ ID NO: 1. The reference teaches that BS106 is expressed specifically in breast tissue and therefore the BS106 gene is considered to be a "BSG". Abbott Laboratories teaches that the BS106 gene can be used to diagnose, stage or monitor the progression of breast cancer and can be used to detect metastatic breast cancer (see for example, pages 3-4). It is stated that samples to be assayed may include blood, urine, saliva and stool. Abbott Laboratories does not specifically exemplify methods in which breast cancer is diagnosed by detecting an increase in the level of nucleic acids encoding BS106. However, in view of the teachings of Abbott Laboratories, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Abbott Laboratories for detecting BS106 nucleic acids to a means for diagnosing breast cancer in order to have provided an effective and rapid means for the early diagnosis of breast cancer and metastatic breast cancer and for determining the stage of breast cancer.

(Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/16811

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12Q 1/68; C12P 19/34; C07H 21/04; A61K 16/00; C07K 15/28; G01N 33/53 and US Cl.: 435/6, 7.1, 91.2;
536/23.5, 24.31; 424/174.1; 530/388.1, 388.8

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claims 6, 8 and 10-14 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest nucleic acids comprising SEQ ID NO :2-4.

Claims 1-14 meet the criteria set out in PCT Article 33(4), for industrial applicability.

_____ NEW CITATIONS _____

NONE

09/762027

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

MAY 30 2000

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NEW JERSEY 08053

Docket System ☒
Status Report ☒
Docket Book ☒

7/26/00

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing
(day/month/year)

26 MAY 2000

Applicant's or agent's file reference

DEX-0040

REPLY DUE

within TWO months
from the above date of mailing

International application No.

PCT/US99/16811

International filing date (day/month/year)

22 JULY 1999

Priority date (day/month/year)

04 AUGUST 1998

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant

DIADEXUS LLC

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04 DECEMBER 2000

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CARLA MYERS

Telephone No. (703) 308-0196

WRITTEN OPINION

International application No.

PCT/US99/16811

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-31, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the claims:

pages 32-34, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the drawings:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:

pages 1-7, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion is drawn on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages None

☒ the claims, Nos. None

☒ the drawings, sheets/fig None

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to be beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

WRITTEN OPINION

International application No.

PCT/US99/16811

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims <u>6-14</u>	YES
	Claims <u>1-5</u>	NO
Inventive Step (IS)	Claims <u>6, 8, 10-14</u>	YES
	Claims <u>1-5, 7, and 9</u>	NO
Industrial Applicability (IA)	Claims <u>1-14</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations

Claims 1-5 lack novelty under PCT Article 33(2) as being anticipated by Watson et al (herein after 'Watson'). Watson teaches methods for diagnosing breast cancer by detecting levels of mammaglobin mRNA in tissues or bodily fluids of a patient and comparing the levels of mammaglobin to those obtained in control, normal tissues or bodily fluids wherein the presence of increased levels of mammaglobin is indicative of the presence of breast cancer (see, for example, col. 6, and 8-9). Watson teaches that mammaglobin is expressed in tumor and normal breast tissue, but is not expressed in non-breast tissues (col. 6). Accordingly, mammaglobin is considered to be a breast specific gene (BSG). Watson (col. 6) further teaches that detection of mammaglobin can be used to diagnose metastatic breast cancer and to stage breast cancer.

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WRITTEN OPINION

International application No.

PCT/US99/16811

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Sheet 10

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12Q 1/68; C12P 19/34; C07H 21/04; A61K 16/00; C07K 15/28; G01N 33/53 and US Cl.: 435/6, 7.1, 91.2; 536/23.5, 24.31; 424/174.1; 530/388.1, 388.8

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claims 6, 8 and 10-14 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest nucleic acids comprising SEQ ID NO :2-4.

Claims 1-14 meet the criteria set out in PCT Article 33(4), for industrial applicability.

----- NEW CITATIONS -----
NONE

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

02 May 2000 (02.05.00)

International application No.

PCT/US99/16811

Applicant's or agent's file reference

DEX-0040

International filing date (day/month/year)

22 July 1999 (22.07.99)

Priority date (day/month/year)

04 August 1998 (04.08.98)

Applicant

SUN, Yongming et al

1. The designated Office is hereby notified of its election made:

☒

in the demand filed with the International Preliminary Examining Authority on:

29 February 2000 (29.02.00)

☐

in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

R. E. Stoffel

Telephone No.: (41-22) 338.83.38